

Introduction

Nearly everyone's life has been directly or indirectly touched by cancer. Most scientists involved in cancer research believe that a significant fraction of all cancers may be associated with the environment in which we live and work. In this context, the environment is defined as anything that interacts with humans, including substances eaten, drunk, and smoked; natural and medical radiation; workplace exposures; drugs; aspects of sexual behavior; and substances in air, water, and soil (OTA, 1981). Although we rarely know the environmental factors and conditions which are responsible for the development of specific cancers, in some cases we have some understanding. It is the firm belief of many scientists who are knowledgeable in these areas that much of the cancer associated with the environment may be avoided (Tomatis et al., 1997).

The people of the United States of America, concerned with the relationships between their environment and cancer have asked, through the U.S. Congress, for information about substances that cause or might cause cancer. Section 262 of Public Law 95-622 of November 9, 1978¹ requests this information, and Section 301 (b) (4) of the Public Health Service Act stipulates that the Secretary of the Department of Health and Human Services, as amended, shall publish a biennial report which contains:

- A) a list of all substances (*i*) which either are known to be carcinogens [in humans] or may reasonably be anticipated to be [human] carcinogens; and (*ii*) to which a significant number of persons residing in the United States are exposed;
- B) information concerning the nature of such exposure and the estimated number of persons exposed to such substances;
- C) a statement identifying (*i*) each substance contained in this list for which no effluent, ambient, or exposure standard has been established by a Federal agency; and (*ii*) for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in this list, the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance; and
- D) a description of (*i*) each request received during the year to conduct research into, or testing for, the carcinogenicity of substances and (*ii*) how the Secretary and each such other entity, respectively, have responded to each request.

The Report on Carcinogens discusses individual substances, mixtures of chemicals, or exposure circumstances associated with technological processes which are known to be human carcinogens or which may reasonably be anticipated to be human carcinogens; they also contain information received from other Federal agencies relating to estimated exposures and exposure standards or guidelines.

The Report on Carcinogens contains a list of substances that may pose a potential hazard to human health. The Reports are informational scientific and public health documents. They serve as meaningful compilations 1) of data on the carcinogenicity of the listed substances in humans and/or animals, 2) on the potential for exposure to these substances, and 3) on the regulations promulgated by Federal agencies to limit exposures. The Reports do not present quantitative assessments of carcinogenic risk. The listing of a substance in the Report, therefore, does not establish that such substance presents a risk to persons in their daily lives. Such formal risk assessments are the purview of the appropriate Federal, State, and local health regulatory and research agencies.

It is also important to note that these listings do not address potential benefits of exposures to certain carcinogenic substances in special situations. For example, numerous drugs that are part of typical cancer chemotherapeutic programs have been shown to increase the frequency of secondary cancers in patients undergoing chemotherapy. In these instances, the benefits of exposure to the substance may well far outweigh the risks entailed and personal decisions concerning voluntary exposures to carcinogenic agents need to be based, at least in part, on information that is beyond the scope of this document.

Identifying Carcinogens

For many years, government research agencies including the National Toxicology Program, industries, academia, and other research organizations have studied various substances to identify those that might cause cancer. Most of this chemical or occupational specific information is published in the scientific literature or in publicly available and peer reviewed technical reports, and is a primary source of information for identifying substances for consideration for listing in these Reports. Many of the agents, substances, and mixtures that are listed in the Report on Carcinogens have also been reviewed and evaluated by other organizations. These include the International Agency for Research on Cancer (IARC) in Lyon, France, the Environmental Protection Agency of the State of California, and other U.S. Federal and International Agencies.

Human and Animal Studies

Both human and animal studies are used to identify chemicals as possible human carcinogens. The strongest evidence for establishing a relationship between exposure to any given chemical and cancer in humans comes from epidemiological studies. These human studies of exposure and cancer must consider the latent period of most cancer development since the exposure to the carcinogen often occurs many years (sometimes 20-30 years or more) before the first sign of cancer appears. However, the most common method to identify potential human carcinogens is the long-term animal bioassay. These bioassays provide accurate information about dose and duration of exposure, and interactions of the substance with other chemicals or modifiers. In these studies, the test agent, substance, or mixture is administered to one or usually two laboratory rodent species over a range of doses and times with all parameters chosen to maximize the possibility of producing cancer.

It is not possible to predict perfectly which agents, substances, or mixtures will be carcinogenic in humans from animal studies alone, but it is true that most human carcinogens do produce cancers in animals when these chemicals are

¹Section 262 of Public Law 95-622, the Community Mental Health Extension Centers Act of 1978, enacted November 9, 1978, added section 301(b)(4) but provided for annual reports. In 1993, the provision was amended to provide for biennial reports.

adequately tested. Experimental carcinogenesis research is based on the scientific assumption that chemicals causing cancer in animals will have similar effects in humans. Strict correspondence of results in humans with those in animals to any adverse response to chemicals (of which cancer is only one) is not always obtained, but laboratory animals remain the best testing tool for detecting potential hazards of all kinds including cancer (OTA, 1981; IARC S.2, 1980; Tomatis et al., 1996).

Listing Criteria

Section 301 (b)(4)(A)(i) of the Public Health Service Act requires a list of all substances which either are known to be carcinogens [in humans] or may reasonably be anticipated to be [human] carcinogens. For the purpose of the first seven Annual Reports on Carcinogens, the degrees of evidence were as follows:

Known to be Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between the agent and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

- A. **There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded, or**
- B. **There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure.**

During 1994, and 1995, the criteria for listing an agent, substance, or mixture in the Report on Carcinogens, or for removing an agent from the listings, were revisited in a series of open public meetings. In recognition of the advances made in understanding the biological events involved in carcinogenesis, it was recommended that the criteria for listing an agent, substance, or mixture be expanded to include a broader array of information related to the carcinogenic process. Thus, the information considered in listing an agent, substance, or mixture would not be restricted to studies showing increases in malignant tumor incidence in experimental animal or epidemiology studies, but other information contributing to a scientific judgment concerning the likelihood that an agent, substance, or mixture would cause cancer in humans would also enter into the decision to list or not to list a chemical. Also at this time, formal procedures for consideration of petitions to remove an agent, substance, or mixture from the listings were adopted (see Appendix C for details of listing and delisting procedures).

The revised criteria for listing a substance in the Report on Carcinogens were approved by the Secretary, HHS on September 13, 1996. The substances newly included in the Eighth Report on

Carcinogens were evaluated using these revised criteria, which are as follows:

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded, or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well defined, structurally-related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Inclusion of Substances

The Eighth Report contains 198 entries, 14 of which have not appeared in earlier reports. This report also contains a reclassification of thiotepa from *Reasonably Anticipated To Be a Human Carcinogen* to *Known To Be a Human Carcinogen*, with the corresponding revision of the earlier entry for this chemical. These 15 new profiles include molecular structures of the substances. In the Ninth Report on Carcinogens, molecular structures, if known, will be included in every profile. The original literature supporting the new listings of substances in the Eighth Report on Carcinogens is compiled in supporting background documents which can be accessed via the internet at <http://ntp-server.niehs.nih.gov/> or by contacting the National Toxicology Program, Report on Carcinogens, MD EC-14,

P.O. Box 12233, Research Triangle Park, NC 27709. For information contact Dr. C. W. Jameson, phone: (919) 541-4096, fax: (919) 541-2242, E-mail: jameson@niehs.nih.gov.

Section II.A lists all the agents, substances, mixtures, or medical treatments identified in Section III of this Report. Section II.A.1 lists in alphabetical order names and synonyms of agents, substances, mixtures, and medical treatments profiled in III.A, *Known To Be a Human Carcinogen*. Section II.A.2 similarly lists those agents, substances, and mixtures profiled in III.B, *Reasonably Anticipated To Be a Human Carcinogen*.

Section III, Substance Profiles, contains brief descriptions of each substance with a summary of evidence for its carcinogenicity. The profiles are divided into two sublists. (See the Table of Contents.) The first sublist, III.A, contains a list of 29 agents, substances, mixtures, or exposure circumstances *Known To Be a Human Carcinogen*. The second sublist of 169 entries, III.B, includes agents, substances, or mixtures which are *Reasonably Anticipated To Be a Human Carcinogen*. References to the original papers on experimental or epidemiological studies, which can be found in the supporting documents, the IARC Monographs or in the NCI and NTP bioassay reports, have not always been included in the Eighth Report.

A substance not listed in this Eighth Report may still be a known carcinogen or reasonably anticipated to be a carcinogen. More substances than those included may present a carcinogenic risk to persons living in the United States. Other substances will be considered for subsequent Reports as data become available.

The Eighth Report on Carcinogens contains entries on the carcinogenicity of seven metals (arsenic, beryllium, cadmium, chromium, lead, nickel, and thorium). The entries for the individual metals identify those compounds of the metal (and, where appropriate, the elemental metal itself) for which evidence of carcinogenicity in exposed humans or experimental animals is considered adequate. Relatively few of the many different forms (elemental, salts, complexes, chelates, etc.) of the metals have been fully evaluated for carcinogenicity. The various factors that influence the carcinogenic potential of a given metal form that should be considered include: route of exposure, absorption, distribution, valence state, metabolism, elimination, as well as potential for specific biochemical interactions in cells. However, in the absence of specific information, a metal shown to be carcinogenic in one of its forms should be considered as being potentially carcinogenic in its other forms.

Ionizing radiation, ultraviolet radiation (including sunlight), tobacco, alcoholic beverages, and some viruses are known or suspected carcinogens. They have not yet been evaluated for inclusion in the Report on Carcinogens and are therefore not included in The Eighth Report on Carcinogens (unless acting in conjunction with a chemical). However, ionizing radiation is discussed thoroughly in a General Accounting Office Report (GAO, 1981); and a Surgeon General's Report and an EPA Report review the overwhelming relationship between tobacco and cancer; (OSH, 1982; EPA, 1992). Reports issued by the National Cancer Institute or the IARC explain the relationship of alcoholic beverages, ultraviolet radiation, and viruses to cancer (e.g., Shimkin, 1980; IARC, 1988; IARC, 1996).

Certain manufacturing processes, occupations, and exposure circumstances have been considered by the International Agency for Research on Cancer (IARC) and have been classified by IARC as sources which are known to be carcinogenic to humans because of the associated increased incidences of cancer in workers in these

settings. The NTP has not yet reviewed the data supporting the listing of these occupational situations as posing a carcinogenic threat to humans, and recognizes that certain aspects of occupational exposures may differ in different parts of the world or may have changed over time. In addition, the manufacturing processes and occupations reviewed by IARC in their determinations may differ greatly from what has been or is currently used in the United States. In the interest of public health and for completeness, these occupational exposures are referenced in Appendix A with the corresponding IARC references given.

Preparation of Reports on Carcinogens

Within the Department of Health and Human Services, the responsibility for preparing these Reports has been delegated by the Secretary to the National Toxicology Program. The process used to prepare the Reports on Carcinogens involves multiple levels of review, both of the substances considered for listing in or delisting from the Reports and of the draft Reports prior to publication. Continuing opportunities for public comment and participation are also an integral part of the process. Listing/Delisting Procedures are described more fully in Section V.

Two Federal scientific review groups and one non-government scientific peer-review body (a subcommittee of the NTP Board of Scientific Counselors) evaluate the substances that are candidates for listing in or delisting from the Reports on Carcinogens. Each group reviews available data relevant both to the carcinogenicity of the substances and to exposure to the substances of persons residing in the United States. The membership of these three review groups may be found in Appendix B, List of Participants.

The first review group is the NIEHS/NTP Report on Carcinogens Review Committee. An agent, substance or mixture petitioned for listing or delisting is announced in the Federal Register, trade journals and NTP newsletters to solicit public comment. The original petition and all comments received are evaluated by this NIEHS/NTP Report on Carcinogens Review Committee composed of scientists from the NIEHS/NTP, to determine if the information provided is sufficient to merit further consideration. If it is determined the petition warrants formal consideration, the NTP may initiate an independent search of the literature and prepare a draft background document for the substance under consideration. This Committee may also propose a list of candidate substances based upon its evaluation of the IARC Monographs, the NTP Technical Reports, and other peer reviewed carcinogenesis studies. The NIEHS/NTP Report on Carcinogens Review Committee places emphasis upon the carcinogenicity and related toxicological and other data, but also reviews information on exposure provided in the study reports and monographs. If it is determined that a petition contains insufficient information to warrant consideration by the NTP, it is returned to the original petitioner, who is invited to resubmit the petition with additional justification, which may include new data, exposure information, etc. A notice, stating the action taken for a petitioned substance found to contain insufficient justification for consideration, is published in the Federal Register, trade journals and NTP newsletters, and included in subsequent editions of the Report with the reason(s) why it was not considered further. This decision is also forwarded to the NTP Board of Scientific Counselors and the NTP Executive Committee. The list of substances recommended by the Committee for addition to the Report is divided into two sections, those substances *Known To Be a Human Carcinogen* and those substances *Reasonably Anticipated To Be a Human Carcinogen*.

The second review group is the Working Group for the Reports on Carcinogens (the Working Group), which is a Subcommittee of the NTP Executive Committee.² This Working Group evaluates the list of candidate substances for listing or delisting and accompanying recommendations from the NIEHS/NTP Report on Carcinogens Review Committee, as well as production/use/exposure profiles on each of the substances.

External peer review of the petitions is performed by a subcommittee of the NTP Board of Scientific Counselors. The Subcommittee reviews petitions in open, public meetings. Prior to public review, a notice is published in the Federal Register, trade journals, and NTP Liaison Office updates, again soliciting public comment. The Notice also invites interested groups or individuals to submit written comments and/or to address the subcommittee during the review meeting. Upon completion of its review, the outside peer review subcommittee provides recommendations for listing or delisting the petitioned agent, substance, or mixture.

The list of proposed substances for listing or delisting is printed in the Federal Register and other appropriate publications at several steps of this process for comment. Final decisions on the substances to be included in the Reports are made after the three review groups have evaluated the submitted comments on each of the issues. The list of substances under consideration for listing in or delisting from the Report on Carcinogens can be obtained from the internet by accessing the National Toxicology Program, home page at <http://ntp-server.niehs.nih.gov> or by contacting the National Toxicology Program, Report on Carcinogens, MD EC-14, P.O. Box 12233, Research Triangle Park, NC 27709. For information contact Dr. C. W. Jameson, phone: (919) 541-4096, fax: (919) 541-2242, E-mail: jameson@niehs.nih.gov.

Substances included in the Report on Carcinogens may be delisted from subsequent Reports for one of two reasons. Either exposure to persons residing in the United States cannot be demonstrated, or new data have been generated that change the overall evaluation of the substance and it no longer meets the criteria to be listed in the Report on Carcinogens. Chemical substances delisted from Reports are included in Section II.B of subsequent Reports along with the reason for delisting.

An agent, substance, or mixture may have been nominated and reviewed for listing in the Report on Carcinogens but not selected for listing because it did not meet the criteria as either a *Known To Be a Human Carcinogen* or *Reasonably Anticipated To Be a Human Carcinogen*. A list of substances evaluated but not listed in the Report on Carcinogens can be obtained from the internet by accessing the National Toxicology Program, home page at <http://ntp-server.niehs.nih.gov> or by contacting the National Toxicology Program, Report on Carcinogens, MD EC-14, P.O. Box 12233, Research Triangle Park, NC 27709. For information contact: Dr. C. W. Jameson, phone: (919) 541-4096, fax: (919) 541-2242, E-mail: jameson@niehs.nih.gov.

²Agencies represented on the NTP Executive Committee include: Agency for Toxic Substances and Disease Registry (ATSDR), Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Center for Environmental Health/ Centers for Disease Control and Prevention (NCEH/CDC), National Center for Toxicological Research (NCTR), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration (OSHA), Department of Health and Human Services (DHHS), National Institutes of Health (NIH), National Cancer Institute (NCI), National Library of Medicine (NLM), and National Institute of Environmental Health Sciences/NTP (NIEHS/NTP).

Estimating Exposure

Section 301 (b)(4)(A)(ii) of the Public Health Service Act requires this Report to include those substances either *Known* or *Reasonably Anticipated To Be a Human Carcinogens* and to which a significant number of people residing in the United States are exposed. Substances to which very few people are exposed are not included for the most part. Some substances that have been banned or restricted in use are contained in the Report (e.g., safrole, arsenical pesticides, mirex), either because people who were previously exposed remain potentially at risk or because these substances are still present in the environment.

Section 301 (b)(4)(B) of the Public Health Service Act requires that the Reports provide Information concerning the nature of such exposure and the estimated number of persons exposed to such substances, i.e., substances either *Known* or *Reasonably Anticipated to be a Human Carcinogen*. Four of the agencies participating with the NTP on the preparation of the Eighth Report; Consumer Product Safety Commission (CPSC), U.S. Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Occupational Safety and Health Administration (OSHA) are responsible for regulating hazardous substances and limiting the exposure to and use of such substances. Most of the information in each entry of the Report on Carcinogens on Use, Production, and Exposure is provided by participants from the regulatory agencies given above. The determination of the number of people potentially exposed and the route, intensity, and duration of such exposure for each substance remains a formidable task. This Report attempts to respond to these questions, and wherever adequate answers could be obtained, they are included in Sections III.A and III.B.

The National Occupational Hazard Survey (NOHS), conducted by CDC/NIOSH from 1972 to 1974, and the National Occupational Exposure Survey (NOES) (1981-1983) have yielded potential exposure data on many of these compounds. Where available, NOES estimates are provided in the profiles on the substances; NOHS figures are also given in some profiles when no other data are available.

Regulatory Status

Section 301 (b)(4)(C)(i) of the Public Health Service Act requires a statement identifying each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency. The Eighth Report responds to this requirement by appending to the description of each substance a summary of Federal regulations promulgated by the participating agencies.³ Some of these standards and regulations have been enacted for reasons other than the carcinogenicity of the substance; for instance, to prevent other adverse health effects or to improve the quality of the environment or food. Solid or liquid wastes or wastes discharged into the air may contain carcinogens, yet these may be regulated as toxic substances or hazardous pollutants and not specifically as carcinogens. If these regulations reduce exposure to carcinogens, then the cancer risk posed by such substances also will likely decrease.

The Regulations tables and text in approximately 25 percent of the substance profiles contained in the full Seventh Report on

³The summary of Federal Regulations is contained in the full Report on Carcinogens. Throughout these volumes recommendations of the National Institute for Occupational Safety and Health (NIOSH) are included in the tables of regulations. While NIOSH is not a regulatory agency, the NIOSH findings are often used for the formulation of regulatory actions.

Carcinogens have been updated in the Eighth Report on Carcinogens. This includes all 29 substances listed as *Known To Be a Human Carcinogen* and the first 21 substances listed as *Reasonably Anticipated To Be a Human Carcinogen*. Each regulatory table that has been updated is followed by a footnote noting the dates and titles of the 1996 Code of Federal Regulations examined. The regulations tables for all of the substance profiles will be updated in the Ninth Report on Carcinogens.

Estimating Risk Reduction

Section 301 (b)(4)(C)(i) of the Public Health Service Act requires a statement identifying for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance. This requires quantified information on the amount of protection from cancer that the public receives from established Federal standards.

Estimating the amount of health protection is perhaps the most difficult task in preparing the Reports. One reason is that most Federal laws concerned with reducing cancer risk have been enacted only within the last 15-20 years. Given the long period between the initial exposure to a carcinogen and the onset of disease, it is still too early to evaluate to what extent Federal standards and other regulations have decreased the human cancer risk. Another reason is that information on past exposure levels, which could serve as a baseline for estimating future risk reduction, often is not available or is inaccurate.

The risk—the probability of developing cancer—depends on many things, including the intensity, route, and duration of exposure to a carcinogen or carcinogens. Individuals may respond differently to similar exposures, depending on host factors such as age, sex, nutritional status, overall health, and inherited characteristics. Only in few instances, where studies of long-term human exposures and cancer incidence in restricted environments are available, can risk be estimated with complete confidence.

One possible way to provide quantitative estimates of risk reduction might be to assume that the cancer risk is directly proportional to exposure. This approach also supposes that data on past and present exposure levels are available, or that conditions in all workplaces are in compliance with regulations. However, information supporting these assumptions is only rarely obtainable. Nevertheless, it is reasonable and prudent to accept that the reduction of exposure, for any reason, particularly to substances shown to be carcinogenic in experimental animals, will decrease the incidence of cancer (Tomatis et al., 1997). This is the basis of current regulatory policies that aim to lower human exposure to cancer-causing substances and thereby improve public health.

Requests for Research, Testing, and Information

Section 301 (b)(4)(D) of the Public Health Service Act requires a description: (1) of each request received during the year involved:

- (I) from a Federal agency outside the Department of Health and Human Services for the Secretary, or
- (II) from an entity within the Department of Health and Human Services to any other entity within the Department, to conduct research into, or testing for, the carcinogenicity of substances or to provide information described in clause (ii) of subparagraph (C), and (2) of how the Secretary and each such

other entity, respectively, have responded to each such request.

Section IV of the Report includes tables listing such requests as received from the participating agencies.

Other Information

Section V of the full Report on Carcinogens contains a cumulative list of Code of Federal Regulations and Federal Register citations. The Report includes seven appendices: Appendix A is a list of Manufacturing Processes, Occupations, and Exposure Circumstances Classified by IARC as Known to be Carcinogenic to Humans. Appendix B is a list of participating agencies and their representatives who collaborated in preparing the Eighth Report. Appendix C is the Report on Carcinogens Listing/Delisting Procedures. Appendices D, E, and F comprise a glossary of terms, a list of acronyms and abbreviations, and a list of units of measurement, respectively, that are used frequently in the Eighth Report. Appendix G is a list of Chemical Abstracts Service (CAS) Registry Numbers (CASRN) of chemical substances listed as carcinogens in this Report. The CASRN index includes the page number where a profile of the substance appears in the Eighth Report and when the substance was first listed in an NTP Report on Carcinogens.

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